Available online at www.sciencedirect.com

SciVerse ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology 51 (2012) 186–191

www.tjog-online.com

Review Article

Prenatal findings and the genetic diagnosis of fetal overgrowth disorders: Simpson-Golabi-Behmel syndrome, Sotos syndrome, and Beckwith-Wiedemann syndrome

Chih-Ping Chen [a,b,c,d,e,f,g,*]

[a] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[b] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[d] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[e] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[f] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*

Accepted 20 May 2011

Abstract

With the advent of prenatal sonography, fetal overgrowth can be easily detected. Prenatal-onset overgrowth can be secondary to normal variants of familial tall stature, familial rapid maturation, diabetic macrosomia, and congenital nesidioblastosis, or prenatal-onset overgrowth can be primary due to pathological overgrowth disorders. This article provides a comprehensive review of the prenatal findings and the genetic diagnosis of some of the pathological prenatal-onset overgrowth disorders, such as Simpson-Golabi-Behmel syndrome, Sotos syndrome, and Beckwith-Wiedemann syndrome.

Keywords: Beckwith-Wiedemann syndrome; fetus; overgrowth; Simpson-Golabi-Behmel syndrome; Sotos syndrome

Introduction

With the advent of prenatal sonography, fetal overgrowth can be easily detected. Prenatal-onset overgrowth can be secondary to normal variants of familial tall stature, familial rapid maturation, diabetic macrosomia, and congenital nesidioblastosis, or prenatal-onset overgrowth can be primary due to pathological overgrowth disorders. This article provides a comprehensive review of the prenatal findings and the genetic diagnosis of some pathological prenatal-onset overgrowth disorders, such as Simpson-Golabi-Behmel syndrome, Sotos syndrome, and Beckwith-Wiedemann syndrome.

* Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail address: cpc_mmh@yahoo.com.

Simpson-Golabi-Behmel syndrome

Simpson-Golabi-Behmel syndrome (SGBS) is an X-linked recessive disorder. Simpson et al [1] first described two maternal male cousins with macrocephaly, coarse face, broad hands, dysplastic fingernails, and apparently normal intelligence. Behmel et al [2] later reported a similar condition in a sibship of several affected males with additional findings that included congenital heart defects, polydactyly, and a high infant mortality rate. Golabi and Rosen [3] also described a family with several affected males with internal organ malformations who died early. Neri et al [4] described an Italian family with three affected males with similar anomalies as previously reported by Simpson et al [1], Behmel et al [2], and Golabi and Rosen [3] and coined the eponym "Simpson-Golabi-Behmel syndrome".

1028-4559/$ - see front matter
doi:10.1016/j.tjog.2012.04.004

SGBS is characterized by pre- and postnatal overgrowth, coarse face, macrocephaly, macrosomia, macroglossia, hypertelorism, dental malocclusion, palatal abnormalities, supernumerary nipples, cryptorchidism, hypospadias, congenital heart defects, diaphragmatic hernia, polydactyly and brachydactyly of the hands, cutaneous syndactyly of the fingers and toes, hypoplasia of finger nails, vertebral segmental defects, renal dysplasia/nephromegaly, diastasis recti/umbilical hernia, enlarged internal organs, and an increased risk (10%) of developing embryonal tumors such as Wilms tumor, hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, and hepatocellular carcinoma [1–6].

SGBS type 1 (SGBS1; OMIM 312870) is a milder form of SGBS. SGBS type 2 (SGBS2; OMIM 300209) is a more severe form of SGBS [7–9]. SGBS1 is caused by a deletion or mutation in the *GPC3* gene (OMIM 300037), which maps to Xq26 [10]. SGBS2 has been associated with mutations in the *CXORF5* gene (OMIM 300170), which maps to Xp22 [9]. The *GPC3* gene encodes glypican 3, which acts as a negative regulator of Hedgehog signaling during development, and loss-of-function mutations in the *GPC3* gene result in the hyperactivation of Hedgehog signaling that ultimately result in overgrowth and cancer [11]. The *CXORF5* gene or *OFD1* gene encodes chromosome X open reading frame 5 (CXORF5) protein, which is required for the formation of primary cilia and left-right axis specification [12–14]. Loss-of-function mutations in the *CXORF5* gene are associated with X-linked dominant oral-facial-digital syndrome type 1 (OFD1; OMIM 311200) [12,13,15], X-linked recessive SGBS2 [9], and X-linked recessive Joubert syndrome type 10 (JBTS10; OMIM 300804) [16]. The detection rate of mutations and deletions in the *GPC3* gene ranges from 37–70.3% in patients with SGBS [17–19]. Veugelers et al [20] reported the deletion of the *GPC3-GPC4* gene cluster in one family with SGBS. *GPC4* (OMIM 300168) maps to Xq26 centromeric to *GPC3* and encodes glypican 4, which plays a role in the control of cell division and growth regulation [20]. Recently, Waterson et al [21] reported the duplication of the *GPC4* gene in the family that was initially described by Golabi and Rosen [3] and suggested that the duplication of *GPC4* may be the cause of SGBS.

Fetuses with SGBS may prenatally manifest with macrosomia, polyhydramnios, elevated maternal serum α-fetoprotein (MSAFP), cystic hygroma, hydrops fetalis, increased nuchal translucency (NT), craniofacial abnormalities, visceromegaly, renal anomalies, congenital diaphragmatic hernia, polydactyly, and a single umbilical artery [7,22–26]. Chen et al [22] reported three affected males with SGBS in a family, and all of these individuals were later found to have the *GPC4* duplication [21]. The first case had an elevated MSAFP level at 22 weeks of gestation. Prenatal ultrasound at 24 weeks of gestation revealed congenital diaphragmatic hernia, cystic hygroma, and cystic ureters/kidneys. Amniocentesis revealed a 46,XY karyotype. The second case was diagnosed with polyhydramnios at 18 weeks of gestation, and prenatal ultrasound showed congenital diaphragmatic hernia and polydactyly. Amniocentesis revealed a 46,XY karyotype. The third case was terminated at 21 weeks of gestation and demonstrated an elevated MSAFP level, cystic hygroma, craniofacial anomalies, congenital diaphragmatic hernia, and a single umbilical artery. Hughes-Benzie et al [23] reported an elevated MSAFP level at 17 weeks of gestation, macrosomia at 19 weeks of gestation, and polyhydramnios at 28 weeks of gestation in a male fetus affected with SGBS. This case also demonstrated a *GPC3* deletion at the 3' end of exon 1 [27]. Yamashita et al [24] reported macrosomia, severe polyhydramnios, large liver, and remarkably enlarged kidneys at 29 weeks of gestation in a male fetus affected with SGBS. The karyotype was 46,XY. Li and McDonald [25] reported an abnormal NT in the first trimester, an elevated MSAFP level at 16 weeks of gestation, macrosomia, polyhydramnios, cleft lip and palate, and an abnormal skull at 30 weeks of gestation in a male fetus affected with SGBS. The fetus also demonstrated a *GPC3* mutation in exon 2 (c.194_206 del) (p.cys65fs). Weichert et al [26] reported a 1-megabase microdeletion in Xq26.2 that encompassed the *GPC3* gene in a fetus with SGBS. The associated prenatal findings in that case included markedly increased NT in the first trimester, macrocephaly, asymmetric bilateral mild ventriculomegaly, down-turned corners of a permanently open mouth, low-set ears, flat facial profile, macrosomia, and polyhydramnios at 22 weeks of gestation. Terespolsky et al [7] reported the case of four maternally related male cousins with SGBS2, which was confirmed to be associated with the SGBS2 locus at Xp22 by linkage analysis [8]. In their report, one male fetus was diagnosed with a renal abnormality on prenatal ultrasound, another male fetus was diagnosed with polyhydramnios at 22 weeks of gestation, and hydrops fetalis was noted in all three liveborn males at birth.

In instances of fetal overgrowth and polyhydramnios in association with other abnormalities, such as congenital diaphragmatic hernia, increased NT, visceromegaly, renal anomalies, postaxial polydactyly, single umbilical artery, and elevated MSAFP, a differential diagnosis of SGBS should be considered. Examination of the mother for evidence of the mild SGBS phenotype, examination of the male family members who demonstrate a positive SGBS phenotype, mutational analysis of *GPC3*, *GPC4*, and *CXORF5*, and array comparative genomic hybridization (aCGH) analysis of genomic imbalance in Xp22 or Xq26 are helpful for genetic diagnosis and counseling.

Sotos syndrome

Sotos syndrome (OMIM 117550) is an autosomal dominant disorder. Sotos et al [28] first described five children with overgrowth, advanced bone age, acromegalic features, high-arched palate, prominent jaw, and mental retardation. Cole and Hughes [29] suggested that the characteristic facial appearance, learning disabilities, and childhood overgrowth are the major diagnostic criteria for Sotos syndrome. Maroun et al [30] first reported a 4-year-old girl with Sotos syndrome and a 46,XX,t(5;15)(q35;q22) karyotype and suggested that 5q35 is the site of the gene that determines Sotos syndrome.

Imaizumi et al [31] later reported a 15-month-old girl with Sotos syndrome and a 46,XX,t(5;8)(q35;q24.1) karyotype and proposed that the gene responsible for Sotos syndrome is located at 5q35. Kurotaki et al [32] subsequently identified *NSD1* as the gene that is disrupted by the 5q35 breakpoint via positional cloning.

Sotos syndrome is characterized by its cardinal features ($\geq$ 90%) that consists of a characteristic facial appearance—including a high broad forehead, an inverted pear-like head, sparse frontotemporal hair, molar flushing, downslanting palpebral fissures, a long face, and a pointed chin—learning disabilities, and overgrowth; the major features ($\geq$ 15%) include advanced bone age, cranial abnormalities on diagnostic computed tomographic scans and magnetic resonance imaging, poor feeding during infancy, neonatal jaundice, hypotonia, seizures, scoliosis, cardiac anomalies, renal anomalies, joint laxity, pes planus, and a slightly increased risk (2.2% or $<$ 3%) of developing neoplasms such as sacrococcygeal teratoma, neuroblastoma, presacral ganglioma, acute lymphoblastic leukemia, small cell lung cancer, Wilms tumor, hepatocellular carcinoma, cardiac/ovarian fibroma, and germ cell tumor [33−36].

Sotos syndrome is caused by a deletion or mutation in the *NSD1* gene (OMIM 606681), which maps to 5q35 [32,37,38]. The *NSD1* gene encodes nuclear receptor set domain protein 1, which enhances androgen receptor transactivation [39]. At least 90% of patients with Sotos syndrome have *NSD1* abnormalities [40,41]. Intragenic mutations cause 27−93% of non-Japanese Sotos syndrome cases and about 12% of Japanese Sotos syndrome cases, and 5q35 microdeletions cause about 50% of Japanese cases and about 10% of non-Japanese Sotos syndrome cases [36,40−51]. However, in about 10% of classic cases of Sotos syndrome, *NSD1* abnormalities are not identified [41]. Most cases with Sotos syndrome arise *de novo*, and familial Sotos syndrome with vertical transmission occurs in $<$ 10% of cases with Sotos syndrome [41,48,52].

Fetuses with Sotos syndrome may prenatally manifest with increased NT, an increased risk of Down syndrome on maternal serum screening, macrocephaly, polyhydramnios, fetal overgrowth, renal abnormalities, and central nervous system abnormalities [53−55]. Chen et al [53] reported macrocephaly, an irregular skull shape, ventriculomegaly, corpus callosum hypoplasia, enlarged cistern magna, overgrowth, unilateral hydronephrosis, and polyhydramnios on prenatal ultrasound in the third trimester in a fetus with familial Sotos syndrome. The pregnancy was associated with an abnormal maternal serum screen that indicated a Down syndrome risk of 1/212 and a 46,XY karyotype for the fetus. Thomas and Lemire [54] reported macrocephaly and an increased Down syndrome risk of 1/8 on the maternal serum screen at 17 weeks of gestation, and macrosomia and polyhydramnios at 34 weeks of gestation in a fetus with familial Sotos syndrome and a frameshift mutation (5712delC) in the *NSD1* gene. Schou et al [55] reported increased NT (7 mm) and large for date on prenatal ultrasound in a fetus with a *de novo* mutation in the *NSD1* gene. Schaefer et al [56] and Gusmão Melo et al [57] reported abnormal neuroimaging findings in all patients with Sotos syndrome. The reported neuroimaging findings included enlargement of the lateral ventricles, trigones, and occipital horns, corpus callosum hypoplasia, persistence of cavum septum pellucidum, cavum vergae, and cavum velum interpositum, enlarged cisterna magna, heterotopias, macrocerebellum, and periventricular leukomalacia [56,57].

In instances of fetal overgrowth, macrocephaly and polyhydramnios in association with other abnormalities, such as renal abnormalities, central nervous system abnormalities, increased NT, and abnormal maternal serum screening results, a differential diagnosis of Sotos syndrome should be considered. Examination of the parents for evidence of the Sotos syndrome phenotype, examination of the family members with positive Sotos syndrome phenotype, mutational analysis of *NSD1*, and molecular cytogenetic analysis of 5q35 microdeletion by fluorescence *in situ* hybridization (FISH) and/or aCGH are helpful for genetic diagnosis and counseling.

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome (BWS; OMIM 130650) is an imprinting disorder. Beckwith [58] and Wiedemann [59] first described an Exomphalos-Macroglossia-Gigantism (EMG) syndrome that was characterized by the clinical findings of exomphalos (omphalocele), macroglossia, and gigantism (macrosomia). Waziri et al [60] first reported two unrelated children with the features of BWS. In their study, one child demonstrated duplication of 11p13-p15 and the other demonstrated duplication of 11p15. They reviewed six other reported cases with partial dup(11p) and identified the features of BWS. The region 11p15 contains the genes associated with BWS.

BWS is characterized by macrosomia, ear creases/pits, macroglossia, omphalocele/umbilical hernia, visceromegaly, hemihypertrophy, cleft palate, adrenocortical cytomegaly, renal medullary dysplasia, nephromegaly, nephrocalcinosis, nephrolithiasis, polyhydramnios, placental mesenchymal dysplasia, placentomegaly, cardiomegaly, structural cardiac anomalies, facial nevus flammeus, hemangiomata, neonatal hypoglycemia, midface hypoplasia, diastasis recti, advanced bone age, and an increased risk (7.5%) of developing embryonal tumors such as Wilms tumor, hepatoblastoma, rhabdomyosarcoma, adrenocortical carcinoma, and neuroblastoma [61−65].

BWS is caused by epigenetic alterations or genomic imbalances at the chromosome 11p15.5 imprinting cluster, which is functionally divided into domain 1 that contains two imprinted genes—*IGF2* (OMIM 147470; which is expressed from the paternal allele) and *H19* (OMIM 103280; which is expressed from the maternal allele)—and domain 2 that contains three imprinted genes—*CDKN1C* (OMIM 600856; which is expressed from the maternal allele), *KCNQ1* (OMIM 607542; which is expressed from the maternal allele), and *KCNQ1OT1* (OMIM 604115; which is expressed from the paternal allele). The *H19*-associated imprinting center 1 (IC1), or differentially methylated region 1 (DMR1), is usually methylated on the paternal chromosome and unmethylated on

the maternal chromosome. The *KCNQ1OT1*-associated imprinting center 2 (IC2), or KvDMR1 or DMR2, is usually methylated on the maternal chromosome and unmethylated on the paternal chromosome and in *cis* it regulates the expression of the maternally expressed imprinted genes in domain 2 [62,64,65]. Analysis of the frequency of genetic abnormalities in patients with BWS has determined the following: loss of methylation at IC2 on the maternal chromosome occurs in 50% of patients; gain of methylation at IC1 on the maternal chromosome occurs in 5% of patients; *CDKN1C* mutations occur in 10% of patients (5% of patients with no family history of BWS and approximately 40% of patients with a positive family history of BWS); paternal uniparental disomy (UPD) of 11p15.5 occurs in 20% of patients; duplication, inversion, or translocation of 11p15.5 occurs in 1% of patients; and submicroscopic genomic alteration within 11p15.5 occurs in an unknown percentage of patients [65].

Fetuses with BWS may prenatally manifest with macrosomia, polyhydramnios, macroglossia, omphalocele, placentomegaly, a long umbilical cord, echogenic kidneys, and pancreatic cystic dysplasia [66]. Reish et al [67] suggested that fetal overgrowth, polyhydramnios, enlarged placenta, and distended abdomen are the constant prenatal findings of BWS. Williams et al [68] suggested that a diagnosis of BWS can be reliably made by the presence of either two major criteria (macroglossia, macrosomia, and abdominal wall defect) or one major criterion plus two minor criteria (nephromegaly/dysgenesis, adrenal cytomegaly, aneuploidy/abnormal loci, and polyhydramnios).

Children conceived by *in vitro* fertilization (IVF) are at an increased risk of developing BWS [69]. Halliday et al [69] suggested that the overall risk of developing BWS in children conceived by IVF is about 1 in 4,000 (4 of 14,894), or nine times greater than that of the general population. Recently, Gomes et al [70] reported abnormal methylation at IC2 (KvDMR1 or DMR2) in clinically normal children who were conceived by assisted reproductive technologies (ARTs). Hypomethylation at IC2 (KvDMR1 or DMR2) was observed in 3 of 18 clinically normal children conceived by ARTs (2 conceived by IVF and 1 by intracytoplasmic sperm injection [ICSI]). Lim et al [71] additionally found that ART may also be associated with disturbed genomic imprinting in the imprinting control regions other than 11p15.5, such as DMRs at 6q24, 7q32, and 15q13. In a study of 25 cases with post-ART BWS, of which 24 cases had an IC2 epimutation (loss of methylation at KvDMR1), they found that the loss of maternal allele methylation at the DMRs at 6q24, 7q32, and 15q13 occurred in 37.5% of post-ART BWS IC2 defect cases compared with 6.4% of non-ART BWS IC2 defect cases. Their finding indicates that more generalized DMR hypomethylation is more frequent in post-ART BWS cases than non-ART BWS cases.

In instances of fetal overgrowth, macrocephaly and polyhydramnios in association with other abnormalities such as macroglossia, omphalocele, placentomegaly, enlargement of the kidneys and adrenal glands, an obstetric history of ART, a differential diagnosis of BWS should be considered. Examination of the parents for evidence of the BWS phenotype, examination of the family members with a positive BWS phenotype, cytogenetic analysis of 11p15.5 chromosome aberrations, such as duplication, inversion, or translocation, mutational analysis of *CDKN1C*, molecular tests for methylation and/or copy number changes in chromosome 11p15.5, such as gain of methylation at *H19*, loss of methylation at IC2 (KvDMR1 or DMR2), or both, and the UPD test for paternal UPD 11p15.5 are helpful for genetic diagnosis and counseling.

Acknowledgments

This work was supported by research grants NSC-97-2314-B-195-006-MY3 and NSC-99-2628-B-195-001-MY3 from the National Science Council and grant MMH-E-100-04 from the Mackay Memorial Hospital, Taipei, Taiwan.

References

[1] Simpson JL, Landey S, New M, German J. A previously unrecognized X-linked syndrome of dysmorphia. Birth Defects Orig Artic Ser XI; 1975:18–24.
[2] Behmel A, Ploch E, Rosenkranz W. A new X-linked dysplasia gigantism syndrome: identical with the Simpson dysplasia syndrome? Hum Genet 1984;67:409–13.
[3] Golabi M, Rosen L. A new X-linked mental retardation overgrowth syndrome. Am J Med Genet 1984;17:345–58.
[4] Neri G, Marini R, Cappa M, Borrelli P, Opitz JM. Simpson-Golabi-Behmel syndrome: an X-linked encephalo-tropho-schisis syndrome. Am J Med Genet 1988;30:287–99.
[5] Neri G, Gurrieri F, Zanni G, Lin A. Clinical and molecular aspects of the Simpson-Golabi-Behmel syndrome. Am J Med Genet 1998;79:279–83.
[6] James A, Culver K, Golabi M. Simpson-Golabi-Behmel syndrome. In: Pagon RA, Bird TD, Dolan CR, Stephens Karen, editors. Gene Reviews. Seattle (WA): University of Washington, Seattle; 1993–2006 Dec 19.
[7] Terespolsky D, Farrell SA, Siegel-Bartelt J, Weksberg R. Infantile lethal variant of Simpson-Golabi-Behmel syndrome associated with hydrops fetalis. Am J Med Genet 1995;59:329–33.
[8] Brzustowicz LM, Farrell S, Khan MB, Weksberg R. Mapping of a new SGBS locus to chromosome Xp22 in a family with a severe form of Simpson-Golabi-Behmel syndrome. Am J Hum Genet 1999;65:779–83.
[9] Budny B, Chen W, Omran H, Fliegauf M, Tzschach A, Wisniewska M, et al. A novel X-linked recessive mental retardation syndrome comprising macrocephaly and ciliary dysfunction is allelic to oral-facial-digital type I syndrome. Hum Genet 2006;120:171–8.
[10] Pilia G, Hughes-Benzie RM, MacKenzie A, Baybayan P, Chen EY, Huber R, et al. Mutations in *GPC3*, a glypican gene, cause the Simpson-Golabi-Behmel overgrowth syndrome. Nat Genet 1996;12:241–7.
[11] Filmus J, Capurro M. The role of glypican-3 in the regulation of body size and cancer. Cell Cycle 2008;7:2787–90.
[12] Ferrante MI, Giorgio G, Feather SA, Bulfone A, Wright V, Ghiani M, et al. Identification of the gene for oral-facial-digital type I syndrome. Am J Hum Genet 2001;68:569–76.
[13] Ferrante MI, Zullo A, Barra A, Bimonte S, Messaddeq N, Studer M, et al. Oral-facial-digital type I protein is required for primary cilia formation and left-right axis specification. Nat Genet 2006;38:112–7.
[14] Ferrante MI, Romio L, Castro S, Collins JE, Goulding DA, Stemple DL, et al. Convergent extension movements and ciliary function are mediated by *ofd1*, a zebrafish orthologue of the human oral-facial-digital type 1 syndrome gene. Hum Molec Genet 2009;18:289–303.
[15] Rakkolainen A, Ala-Mello S, Kristo P, Orpana A, Jarvela I. Four novel mutations in the *OFD1 (Cxorf5)* gene in Finnish patients with oral-facial-digital syndrome 1. J Med Genet 2002;39:292–6.

[16] Coene KLM, Roepman R, Doherty D, Afroze B, Kroes HY, Letteboer SJF, et al. *OFD1* is mutated in X-linked Joubert syndrome and interacts with *LCA5*-encoded lebercilin. Am J Hum Genet 2009;85: 465–81.
[17] Li M, Shuman C, Fei YL, Cutiongco E, Bender HA, Stevens C, et al. *GPC3* mutation analysis in a spectrum of patients with overgrowth expands the phenotype of Simpson-Golabi-Behmel syndrome. Am J Med Genet 2001;102:161–8.
[18] Veugelers M, Cat BD, Muyldermans SY, Reekmans G, Delande N, Frints S, et al. Mutational analysis of the *GPC3/GPC4* glypican gene cluster on Xq26 in patients with Simpson-Golabi-Behmel syndrome: identification of loss-of-function mutations in the *GPC3* gene. Hum Mol Genet 2000;9:1321–8.
[19] Lin AE, Neri G, Hughes-Benzie R, Weksberg R. Cardiac anomalies in the Simpson-Golabi-Behmel syndrome. Am J Med Genet 1999;83: 378–81.
[20] Veugelers M, Vermeesch J, Watanabe K, Yamaguchi Y, Marynen P, David G. *GPC4*, the gene for human K-glypican, flanks *GPC3* on xq26: deletion of the *GPC3-GPC4* gene cluster in one family with Simpson-Golabi-Behmel syndrome. Genomics 1998;53:1–11.
[21] Waterson J, Stockley TL, Segal S, Golabi M. Novel duplication in glypican-4 as an apparent cause of Simpson-Golabi-Behmel syndrome. Am J Med Genet 2010;152A:179–81.
[22] Chen E, Johnson JP, Cox VA, Golabi M. Simpson-Golabi-Behmel syndrome: congenital diaphragmatic hernia and radiologic findings in two patients and follow-up of a previously reported case. Am J Med Genet 1993;46:574–8.
[23] Hughes-Benzie RM, Tolmie JL, McNay M, Patrick A. Simpson-Golabi-Behmel syndrome: disproportionate fetal overgrowth and elevated maternal serum alpha-fetoprotein. Prenat Diagn 1994;14:313–8.
[24] Yamashita H, Yasuhi I, Ishimaru T, Matsumoto T, Yamabe T. A case of nondiabetic macrosomia with Simpson-Golabi-Behmel syndrome: antenatal sonographic findings. Fetal Diagn Ther 1995;10:134–8.
[25] Li CC, McDonald SD. Increased nuchal translucency and other ultrasound findings in a case of Simpson-Golabi-Behmel syndrome. Fetal Diagn Ther 2009;25:211–5.
[26] Weichert J, Schröer A, Amari F, Siebert R, Caliebe A, Nagel I, et al. A 1Mb-sized microdeletion Xq26.2 encompassing the GPC3 gene in a fetus with Simpson-Golabi-Behmel syndrome: report, antenatal findings and review. Eur J Med Genet 2011;54:343–7.
[27] Hughes-Benzie RM, Pilia G, Xuan JY, Hunter AGW, Chen E, Golabi M, et al. Simpson-Golabi-Behmel syndrome: genotype/phenotype analysis of 18 affected males from 7 unrelated families. Am J Med Genet 1996; 66:227–34.
[28] Sotos JF, Dodge PR, Muirhead DD, Crawford JD, Talbot NB. A syndrome of excessively rapid growth and acromegalic features and a nonprogressive neurologic disorder. N Engl J Med 1964;271: 109–16.
[29] Cole TR, Hughes H. Sotos syndrome: a study of the diagnostic criteria and natural history. J Med Genet 1994;31:20–32.
[30] Maroun C, Schmerler S, Hutcheon RG. Child with Sotos phenotype and a 5:15 translocation. Am J Med Genet 1994;50:291–3.
[31] Imaizumi K, Kimura J, Matsuo M, Kurosawa K, Masuno M, Niikawa N, et al. Sotos syndrome associated with a de novo balanced reciprocal translocation t(5;8)(q35;q24.1). Am J Med Genet 2002;107:58–60.
[32] Kurotaki N, Imaizumi K, Harada N, Masuno M, Kondoh T, Nagai T, et al. Haploinsufficiency of *NSD1* causes Sotos syndrome. Nat Genet 2002;30:365–6.
[33] Cohen Jr MM. Tumors and nontumors in Sotos syndrome. Am J Med Genet 1999;84:173–5.
[34] Baujat G, Cormier-Daire V. Sotos syndrome. Orphanet J Rare Dis 2007; 2:36.
[35] Tatton-Brown K, Rahman N. Sotos syndrome. Eur J Hum Genet 2007;15: 264–71.
[36] Tatton-Brown K, Cole TRP, Rahman N. Sotos syndrome. In: Pagon RA, Bird TD, Dolan CR, Stephens Karen, editors. Gene Reviews. Seattle (WA): University of Washington, Seattle; 1993–2004 [updated December 10, 2009].
[37] Kurotaki N, Harada N, Yoshiura K, Sugano S, Niikawa N, Matsumoto N. Molecular characterization of *NSD1*, a human homologue of the mouse Nsd1 gene. Gene 2001;279:197–204.
[38] Niikawa N. Molecular basis of Sotos syndrome. Horm Res 2004; 62(Suppl. 3):60–5.
[39] Wang X, Yeh S, Wu G, Hsu C-L, Wang L, Chiang T, et al. Identification and characterization of a novel androgen receptor coregulator ARA267-α in prostate cancer cells. J Biol Chem 2001;276:40417–23.
[40] Türkmen S, Gillessen-Kaesbach G, Meinecke P, Albrecht B, Neumann LM, Hesse V, et al. Mutations in *NSD1* are responsible for Sotos syndrome, but are not a frequent finding in other overgrowth phenotypes. Eur J Hum Genet 2003;11:858–65.
[41] Tatton-Brown K, Douglas J, Coleman K, Baujat G, Cole TRP, Das S, et al. Genotype-phenotype associations in Sotos syndrome: an analysis of 266 individuals with *NSD1* aberrations. Am J Hum Genet 2005;77: 193–204.
[42] Douglas J, Hanks S, Temple IK, Davies S, Murray A, Upadhyaya M, et al. *NSD1* mutations are the major cause of Sotos syndrome and occur in some cases of Weaver syndrome but are rare in other overgrowth phenotypes. Am J Hum Genet 2003;72:132–43.
[43] Rio M, Clech L, Amiel J, Faivre L, Lyonnet S, Le Merrer M, et al. Spectrum of *NSD1* mutations in Sotos and Weaver syndromes. J Med Genet 2003;40:436–40.
[44] Cecconi M, Forzano F, Milani D, Cavani S, Baldo C, Selicorni A, et al. Mutation analysis of the *NSD1* gene in a group of 59 patients with congenital overgrowth. Am J Med Genet 2005;134A:247–53.
[45] Faravelli F. *NSD1* mutations in Sotos syndrome. Am J Med Genet C Semin Med Genet 2005;137C:24–31.
[46] Melchior L, Schwartz M, Duno M. dHPLC screening of the *NSD1* gene identifies nine novel mutations—summary of the first 100 Sotos syndrome mutations. Ann Hum Genet 2005;69:222–6.
[47] Waggoner DJ, Raca G, Welch K, Dempsey M, Anderes E, Ostrovnaya I, et al. *NSD1* analysis for Sotos syndrome: insights and perspectives from the clinical laboratory. Genet Med 2005;7:524–33.
[48] Kurotaki N, Harada N, Shimokawa O, Miyake N, Kawame H, Uetake K, et al. Fifty microdeletions among 112 cases of Sotos syndrome: low copy repeats possibly mediate the common deletion. Hum Mutat 2003;22:378–87.
[49] Miyake N, Kurotaki N, Sugawara H, Shimokawa O, Harada N, Kondoh T, et al. Preferential paternal origin of microdeletions caused by prezygotic chromosome or chromatid rearrangements in sotos syndrome. Am J Hum Genet 2003;72:1331–7.
[50] Tei S, Tsuneishi S, Matsuo M. The first Japanese familial Sotos syndrome with a novel mutation of the *NSD1* gene. Kobe J Med Sci 2006;52:1–8.
[51] Saugier-Veber P, Bonnet C, Afenjar A, Drouin-Garraud V, Coubes C, Fehrenbach S, et al. Heterogeneity of *NSD1* alterations in 116 patients with Sotos syndrome. Hum Mutat 2007;28:1098–107.
[52] Höglund P, Kurotaki N, Kytola S, Miyake N, Somer M, Matsumoto N. Familial Sotos syndrome is caused by a novel 1 bp deletion of the *NSD1* gene. J Med Genet 2003;40:51–4.
[53] Chen CP, Lin SP, Chang TY, Chiu NC, Shih SL, Lin CJ, et al. Perinatal imaging findings of inherited Sotos syndrome. Prenat Diagn 2002;22: 887–92.
[54] Thomas A, Lemire EG. Sotos syndrome: antenatal presentation. Am J Med Genet 2008;146A:1312–3.
[55] Schou KV, Kirchhoff M, Nygaard U, Jørgensen C, Sundberg K. Increased nuchal translucency with normal karyotype: a follow-up study of 100 cases supplemented with CGH and MLPA analyses. Ultrasound Obstet Gynecol 2009;34:618–22.
[56] Schaefer GB, Bodensteiner JB, Buehler BA, Lin A, Cole TRP. Neuroimaging findings in Sotos syndrome. Am J Med Genet 1997;68:462–5.
[57] Gusmão Melo D, Pina-Neto JM, Acosta AX, Daniel J, de Castro V, Santos AC. Neuroimaging and echocardiographic findings in Sotos syndrome. Am J Med Genet 2000;90:432–4.
[58] Beckwith JB. Extreme cytomegaly of the adrenal fetal cortex, omphalocele, hyperplasia of kidneys and pancreas, and Leydig-cell hyperplasia: Another syndrome? Los Angeles: [Western Society for Pediatric Research abstract]; 1963; Nov 11.

[59] Wiedemann HR. Complexe malformatif familial avec hernie ombilicale et macroglossia, un 'syndrome nouveau. J Genet Hum 1964;13:223–32.
[60] Waziri M, Patil SR, Hanson JW, Bartley JA. Abnormality of chromosome 11 in patients with features of Beckwith-Wiedemann syndrome. J Pediatr 1983;102:873–6.
[61] Weksberg R, Shuman C, Smith AC. Beckwith-Wiedemann syndrome. Am J Med Genet C Semin Med Genet 2005;137C:12–23.
[62] Weksberg R, Shuman C, Beckwith JB. Beckwith-Wiedemann syndrome. Eur J Hum Genet 2010;18:8–14.
[63] Chen CP. Syndromes and disorders associated with omphalocele, I: Beckwith-Wiedemann syndrome. Taiwan J Obstet Gynecol 2007;46:96–102.
[64] Choufani S, Shuman C, Weksberg R. Beckwith-Wiedemann syndrome. Am J Med Genet C Semin Med Genet 2010;154C:343–54.
[65] Shuman C, Beckwith JB, Smith AC, Weksberg R. Beckwith-Wiedemann syndrome. In: Pagon RA, Bird TD, Dolan CR, Stephens Karen, editors. Gene Reviews. Seattle (WA): University of Washington, Seattle; 1993–2000 Mar 3 [updated 2010 Dec 14].
[66] Vora N, Bianchi DW. Genetic considerations in the prenatal diagnosis of overgrowth syndromes. Prenat Diagn 2009;29:923–9.
[67] Reish O, Lerer I, Amiel A, Heyman E, Herman A, Dolfin T, et al. Wiedemann-Beckwith syndrome: further prenatal characterization of the condition. Am J Med Genet 2002;107:209–13.
[68] Williams D, Gauthier DW, Maizels M. Prenatal diagnosis of Beckwith-Wiedemann syndrome. Prenat Diagn 2005;25:879–84.
[69] Halliday J, Oke K, Breheny S, Algar E. Beckwith-Wiedemann syndrome and IVF: a case-control study. Am J Hum Genet 2004;75:526–8.
[70] Gomes MV, Huber J, Ferriani RA, Amaral Neto AM, Ramos ES. Abnormal methylation at the KvDMR1 imprinting control region in clinically normal children conceived by assisted reproductive technologies. Mol Hum Reprod 2009;15:471–7.
[71] Lim D, Bowdin SC, Tee L, Kirby GA, Blair E, Fryer A, et al. Clinical and molecular genetic features of Beckwith-Wiedemann syndrome associated with assisted reproductive technologies. Hum Reprod 2009; 24:741–7.